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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/768,350	HE ET AL.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the First Action on the Merits filed January 18, 2005 is acknowledged.

Claims 1-8 are amended. Claims 9-11 are canceled.

Claims 1-8 are under consideration.

Withdrawn Rejections

35 U.S.C. § 112, 1st paragraph

The rejection under 35 U.S.C. § 112, first paragraph, for claims 1-8 has been withdrawn. Applicant has entered a deposit of two C57 ES cell lines, IC1 and IAC1. Applicant also has amended claims 3-8.

35 U.S.C. § 102(b)

The rejection under 35 U.S.C. § 102 (b) for claims 1-5 are withdrawn. Applicant has amended the claims.

New and Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1, 2, 4, 5, 7, 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 2 is directed to a B6 ES cell line from C57BL/6-Tyr $^{c-23}$ mouse strain. However, the specification does not provide any teachings of a "c-23" strain.

Claims 1, 2, 4, 5, 7, 8 use the name "B6" ES cell line. However, the name of this cell line was not taught in the specification. Furthermore, the specification does not teach how to introduce B6 cells into C57 blastocysts.

It is noted that the terms "c-23" and "B6" were introduced in the claims filed with the amendment, January 18, 2005. However, Applicant did not explicitly or implicitly indicate where the support for the terms was presented in the specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 3, 6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 uses the phrase, "B6 ES cell line form C57BL/6 mouse strain." "Form" appears to be a typographical error.

Claim 2 is missing words that clarify the claim. The phrase, "white albino B6 line from C57BL/6J $^{c-23}$ mouse strain" is unclear.

Claim 3 uses the phrase "said mouse (lines 3-4)." However, the antecedent basis of the mouse in line 4 is unclear because said mouse could refer to the chimeric mouse (line 1) or to a genetically modified mouse in lines 2-3. These two mice are made by different methods. Claim 3 also uses the phrase, "which cannot been seen by coat color." This is incorrectly written because it suggests that depending on the coat color of the mouse, the mouse is invisible.

Claim 6 uses the phrase, "identifiable by coar color (line 4)." "Coar" appears to be a typographical error.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schuster-Gossler et al. (2001, BioTechniques, 31: 1022-1026, see IDS) and Smith (2001, Annu. Rev. Cell Dev. Biol., 17: 435-462, see IDS) in view of Kitayama et al. (2001, Biochemical and Biophysical Research Communications, 281: 1134-1140).

Schuster-Gossler, et al. teach that while gene-targeted mice by means of homologous recombination are a valuable tool, the efficient production of them have not always been met. One reason for this inefficiency results from finding the best host blastocyst/ES cell line combination that yields chimeric animals with germline transmission. To generate a transgenic animal, one would carry out the genetic manipulation in the ES cell, introduce the ES cell into a host blastocyst and allow the embyro to develop into a chimeric animal. One way of discriminating whether a cell originated from an ES cell or the blastocyst host is via a genetic marker of the cell, e.g. coat color. Because some ES/transgenic cells may have become germline cells, one would breed the chimeric animal and select the mice that have been derived from the ES cells. Schuster-Gossler, et al. isolated ES cells from C57BL/6J (B6) mice (page 1022, second column, "B6 ES Cell Derivation and Culture," lines 1-8). B6 ES cells that had gone through 9-17 passages were thawed from liquid nitrogen and then injected into blastocyts from a coisogenic mouse, c^{2J}, or a noncoisogenic mouse, FVB (page 1022, third column, "Generation of Chimeric Mice," lines 1-9. Coat color was used to determine whether the cells had come from the ES cell (black) or from the blastocyst (white). The male mosaic mice were then mated to c^{2J} female mice to determine the germline transmission (page 1023, third column, first paragraph, lines 7-11). The ability of the host blastocyst to colonize ES cells was determined. It was found that when the B6 ES cells were injected into the coisogenic blastocyst, more mice had a higher degree of chimerism that had been contributed by the ES cell (i.e., more of their body was black). When the

chimeric mice were bred, all but one mouse that were made with B6 ES cell/c^{2J} blastocyst (coisogenic), i.e. the same genetic background had had ES-derived offspring (black). However, only 2 of 14 mice made from B6 ES/FVB blastocyst (non-coisogenic) produced ES cell-derived mice (page 1025, second column, lines 17-21). Furthermore, coisogenic mice were transmitting the ES lineage more frequently than the non-coisogenic mice (page 1025, second column, line 22 to third column, line 7). While Schuster-Gossler et al. teach that other strains of mice can be used to generate transgenic mice and that using host blastocysts that are coisogenic with the ES cell produces more viable ES cell-derived mice. However, Schuster-Gossler et al. do not teach how to make transgenic mice.

In addition to the teachings of Schuster-Gossler, et al., Smith teaches that C57BL/6 blastocysts are good blastocysts to use in generating chimeric mice because transgenic mice generated from C57BL/6 blastocysts are comprised of high ES cell contribution and increased frequency of germ line transmission (Smith, page 438, 2nd parag. under "Embryonic Stem Cell-Derived Mice," lines 12-16).

Kitayama et al. teach how to make transgenic mice using C57BL/6 ES cells. Kitayama et al. teach that C57BL/6 ES cells were electroporated with a targeting vector pD2CPRTVS, which was comprised of a Cre gene and a mutated ligand binding domain of the human progesterone receptor gene. For selection of ES cells that underwent homologous recombination, the neo gene was used (Kitayama, et al., page 135-1136, Materials and Methods, "Targeting vector construction" and "ES cell culture").

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to introduce a transgene into a C57BL/6 ES cell in a method taught by Kitayama et al. and to implant C57BL/6 ES cell comprising the transgene into a C56BL/6 blastocyst, in a method taught by Schuster-Gossler et al.

One having ordinary skill in the art would have been motivated to inject a C57BL/6 ES cell comprising a transgene into a C57BL/6 blastocyst, as taught by Schuster-Gossler, et al., in order to obtain a transgenic C57BL/6 mouse. Further motivation is provided by the teachings of Smith that ES cells contribute more to the mosaicism of transgenic mice and thus increase the frequency of germ line transmission.

There would have been a reasonable expectation of success given the results of Kitayama et al. teaching that a transgene construct could be introduced to C57BL/6 ES cells, in order to generate transgenic mice, and the results of Schuster-Gossler, et al. for teaching that C57BL/6 chimeric mice are more often generated when the ES cell and blastocyst are both from the C57BL/6 strain. A reasonable expectation of success that one will obtain the transgenic mouse is also apparent as Smith teaches that mice grown from a C57BL/6 blastocyst are more likely to be comprised of the ES cell and that there is increased frequency that germ line transmission occurs when using a C57BL/6 blastocyst.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

With regards to the issue concerning coat color as being encompassed by the claims, it is noted that the art does not teach the making of transgenic mice wherein the source of the ES cell and blastocyst are from mice that have the same coat color. However, neither the specification nor the art teaches any biological reason why an artisan would preferentially select coat color for generating transgenic mice. Neither the specification nor the art teach that coat color is one of the reasons that an artisan cannot generating transgenic mice, nor does the art or specification teach that coat color is the basis for gross variation of phenotypes between mice comprising a disruption in a gene of interest. It is understood in the art that using ES cells and blastocysts from different colored mice is a rapid way of identifying the lineage of the generated tissue of the mouse. However, no guidance has been provided for why an artisan would generate a "black into black combination," "black into white," "white into black" mouse that is different from generating any transgenic mouse of any colored coat. While the Examiner has considered the Applicant's argument regarding coat color, as it applies to the Applicant overcoming the teachings of Schuster-Gossler (Applicant's Response, page 7, 5th paragraph), wherein unlike Schuster-Gossler, who uses white mice with a tyrosine mutation, wherein the tyrosine mutation has to be bred out of the mice, the Applicant does not provide evidence that teaches an artisan that the mice with the tyrosine mutation has deleterious effects on studying the phenotypes of a knockout mouse generated using blastocysts from C57BL/6J-Tyr $^{c-2J}$ mice. The Applicant also points out that Schuster-Gossler states that the C57BL/6J-Tyr $^{c-2J}$ mice have low blastocyst

production (Schuster-Gossler et al., page 1026, 1st col., last parag.). However, Schuster-Gossler then states that despite the low production of blastocysts, "adequate numbers can be obtained (Schuster-Gossler et al., page 1026, 1st col., last parag.)." As it stands, the Examiner has not given any patentable weight to coat color. Unless the Applicant directs the Examiner to evidence as to why an artisan would generate a transgenic mouse comprising specific coat color, the C57BL/6 transgenic mouse generated by the Applicants are like any other C57BL/6 transgenic mouse.

Response to Arguments

Applicant's arguments with respect to claims 1-8 have been considered but are moot in view of the new ground(s) of rejection. The Examiner has written a new 103 rejection.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH

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SUPERVISORY PATENT EXAMINER